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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,514	04/30/2001	K. Roger Aoki	D2929CON	3428

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,514	AOKI ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,9,17,24,25 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8, 9,17,24,25 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 28, 2006 has been entered. Applicant's amendment is acknowledged. Claims 1, 17 and 30-31 have been amended. Claims 2-7, 10-16, 18-23, 26-27 and 32-33 have been cancelled.

Rejections Withdrawn

2. In view of Applicant amendment the following rejections are withdrawn:

a) rejection of claims 1-9 under 35 U.S.C. 103(a), pages 2-5, paragraph 3 of the previous Office action.

b) rejection of claims 17-25 and 28-33 under 35 U.S.C. 103(a), pages 5-8, paragraph 4 of the previous Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1 and 8-9 are rejected under 35 U.S.C. 103(a) as unpatentable over Anderson et al *(Journal of the Royal Society of Medicine, Volume 85, September 1992)* in view of Sugiyama et al *(Microbiological Reviews, September 1980, p. 419-448).*

The claims are drawn to a method of treating a patient suffering from a neuromuscular disorder or condition said method comprising the steps of administering simultaneously to the patient a therapeutically effective amount of at least two neurotoxins selected from the group consisting of botulinum toxin types A and a botulinum toxin selected from the group consisting of botulinum toxin types B and E, the combination of at least two neurotoxins including an amount of each selected neurotoxin such that the combination is effective in providing an enhancement of relief of muscle contraction for a short duration and long term relief for treating the neuromuscular disorder or condition.

Anderson et al teach a method of treating a patient suffering from spasmodic torticollis comprising administering botulinum toxin A (pages 524-525). Anderson et al teach that three patients developed resistance to the botulinum A treatment and had

developed neutralizing antibodies to the botulinum toxin in their serum (page 528). Anderson et al teach that the presence of antibodies does not necessarily preclude further successful botulinum toxin treatment as one patient attending the study who had a high titre of neutralizing antibody responded again when the treatment dose was increased (page 528).

Anderson et al do not teach that treatment of a neuromuscular disorder or condition comprising administering botulinum toxin A in combination with botulinum toxin types B or E.

Sugiyama et al teach that the antigenically different botulinum neurotoxins have molecular similarities that would be expected of molecules which have a common unique pharmacological action (page 427). Sugiyama et al teach that there is an inverse relationship between specific toxicities and the size of the complexes of a particular toxin type (page 426). Sugiyama et al teach that botulinum toxin type B can be proteolytic (comprises both M and L complexes) or non-proteolytic (comprises only M complexes) (page 426). Sugiyama et al teach that botulinum toxin E comprises only M complexes (page 426). Sugiyama et al teach that purified toxins are more easily detoxified that those in the M complexes (page 427). Sugiyama et al suggest that synaptosomal receptors to which botulinum toxin types bind may not be the same for all toxin types (page 436).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine botulinum toxin type A as taught by Anderson et al and Botulinum toxin type B or E as taught by Sugiyama et al in the

method of treating patients against torticollis because Sugiyama et al suggest that synaptosomal receptors to which botulinum toxin types bind may not be the same for all toxin types (page 436). Therefore, one of ordinary skill in the art would conclude that a combination of botulinum toxin types would have different affinities on the synaptosomal receptors and thereby be more effective in treating a neuromuscular disorder by blocking the synaptosomal receptors at different areas. The inhibiting or blocking acetylcholine release will leave muscles unable to respond to stimuli that reach them via the motor nerves. It would be expected barring evidence to the contrary that administering a combination of botulinum toxin types A and B or A and E would be effective in treating a neuromuscular disorder such as spasmodic torticollis because Sugiyama et al teaches that botulinum toxin types B and E can contain only M complexes and these complexes are less likely to become detoxified than purified botulinum toxin.

Additionally, In re Nilssen (7 USPQ 2d 1500) states:

> ...The board attributes to the "hypothetical person" knowledge of all prior art in the filed of the inventor's endeavor and of the prior art solutions for a common problem even if outside that field.
>
> We reject that recommendation as contrary to our precedent, which holds that for the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references.

Moreover, MPEP at section 2144.06 states

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing

> together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti,25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....

Therefore, "it is *prima facie* obvious to combine two compositions each of which is taught in the art to be used for the very same purpose: idea of combining them flows logically from their having been individually taught in the prior art".

4. Claims 17, 24-25 and 28-31 are rejected under 35 U.S.C. 103(a) as unpatentable over Anderson et al *(Journal of the Royal Society of Medicine, Volume 85, September 1992)* in view of Sugiyama et al *(Microbiological Reviews, September 1980, p. 419-448).*

The claims are drawn to composition comprising therapeutically effective amount of a combination of at least two neurotoxins said combination comprising a botulinum toxin type 1(?, maybe A), and a botulinum toxin selected from the group consisting of types B and E. To provide compact prosecution, the Examiner interprets botulinum toxin 1 to mean botulinum toxin type A.

Anderson et al *(Journal of the Royal Society of Medicine, Volume 85, September 1992)* teach a composition comprising botulinum toxin A to treat patients suffering from

spasmodic torticollis (pages 524-525). Anderson et al teach that three patients developed resistance to the botulinum A treatment and had developed neutralizing antibodies to the botulinum toxin in their serum (page 528). Anderson et al teach that the presence of antibodies does not necessarily preclude further successful botulinum toxin treatment as one patient attending the study who had a high titre of neutralizing antibody responded again when the treatment dose was increased (page 528).

Anderson et al do not teach that treatment of a neuromuscular disorder or condition comprising administering botulinum toxin A in combination with botulinum toxin types B or E.

Sugiyama et al *(Microbiological Reviews, September 1980, p. 419-448)* teaches that the antigenically different botulinum neurotoxins have molecular similarities that would be expected of molecules which have a common unique pharmacological action (page 427). Sugiyama et al teach that there is a inverse relationship between specific toxicities and the size of the complexes of a particular toxin type (page 426). Sugiyama et al teach that botulinum toxin type B can be proteolytic (comprises both M and L complexes) or non-proteolytic (comprises only M complexes) (page 426). Sugiyama et al teach that botulinum toxin E comprises only M complexes (page 426). Sugiyama et al teach that purified toxins are more easily detoxified that those in the M complexes (page 427). Sugiyama et al suggest that synaptosomal receptors to which botulinum toxin types bind may not be the same for all toxin types (page 436). Claim limitations such as "for treating a patient suffering from a neuromuscular disorder or condition", "the combination is effective in providing an enhancement of relief of muscle contraction

for a short duration, long term relief for treating the neuromuscular disorder or condition", "wherein the duration of therapeutic activity is suitable for the treatment of joint dislocations, relaxation for physical therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery", for the prevention of muscle contractions prior to or after surgery", "wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair" and "treatment of scoliosis and spasm of sphincter muscles" are being viewed as limitations of intended use.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combination of botulinum toxin type A as taught by Anderson et al and botulinum toxin type B or E as taught by Sugiyama et al in the method of treating patients against a neuromuscular disorder because Sugiyama et al suggest that synaptosomal receptors to which botulinum toxin types bind may not be the same for all toxin types (page 436). Therefore, one of ordinary skill in the art would conclude that a combination of botulinum toxin types would have different affinities on the synaptosomal receptors and thereby be effective in treating a neuromuscular disorder by blocking the synaptosomal receptors at different areas. Thus, inhibiting or blocking acetylcholine release which leaves muscles unable to respond to stimuli that reach them via the motor nerves. It would be expected barring evidence to the contrary that administering a combination of botulinum toxin types A and B or A and E would be effective in treating a neuromuscular disorder such as spasmodic torticollis because Sugiyama et al teach that botulinum toxin types B and E can contain only M complexes and these complexes are less likely to become detoxified than purified botulinum toxin.

Additionally, In re Nilssen (7 USPQ 2d 1500) states:

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"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti,25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....

Therefore, "it is *prima facie* obvious to combine two compositions each of which is taught in the art to be used for the very same purpose: idea of combining them flows logically from their having been individually taught in the prior art".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 17 and 24-25 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 17 and 24-25 recite the limitation "botulinum toxin type 1". It is unclear as to what Applicant is referring. Correction and/or clarification is required.

6. Claim 30-31 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 31 recites the limitation "wherein the amount of botulinum toxin A is greater than the amount of the second neurotoxin". It is unclear as to what dosages of botulinum toxin are being administered. What kind of "amount" is administered in the "therapeutic composition". Correction and/or clarification is required.

Status of Claims

7. No claims are allowed.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (571)272-8300.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
May 7, 2006

NITA MINNIFIELD
PRIMARY EXAMINER